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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/963,288	11/03/97	NORSTEDT G	10806-48

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EXAMINER	
BAKER, A	
ART UNIT	**PAPER NUMBER**
1632	16

DATE MAILED: 04/26/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/963,288	Norstedt et al.
Examiner	**Group Art Unit**
Anne-Marie Baker, Ph.D.	1632

☒ Responsive to communication(s) filed on *Mar 21, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 2, 5, 7-11, 15-17, 19-36, and 39-48* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 5, 7-11, 15-17, 19-36, and 39-48* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☒ received in Application No. (Series Code/Serial Number) *08/809,256*.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed March 21, 2000 (Paper No. 15) has been entered. Claims 6, 37, and 38 have been cancelled. Claims 1, 5, 8, 19, 23, 25, 26, 27, 29, and 34 have been amended. Claims 39-48 have been newly added.

Claims 1, 2, 5, 7-11, 15-17, 19-36, and 39-48 are pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous Office Action are hereby withdrawn.

Claim Objections

Claims 25-29 and 34-36 are objected to because of the following informalities: The sequences recited in the claims are not identified by SEQ ID NO. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 19-22, 34-36, 39, 40, and 44-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 2, 19-22, 34-36, 39, 40, and 46-48 are directed to an *in vitro* method of enhancing the transcription of a gene.

The specification fails to provide an enabling disclosure for the method of enhancing transcription *in vitro* because the specification does not teach targeting methods that would be required to integrate an enhancer element in a DNA construct that has already been incorporated into the genome of a eukaryotic host cell. The claims require that the enhancer element be placed upstream of a promoter that is already present in the genome of the host cell. This requires gene targeting methods that are not described in the specification. Furthermore, the specification does not teach a selection step for identifying and isolating a clone with the enhancer integrated at the desired position. Thus, one of skill in the art would not know how to incorporate the enhancer element at the desired position (upstream of the promoter) because gene targeting methods typically require a selection step for identification of cells that have undergone a homologous recombination event. This requires insertion of a selectable marker such as an antibiotic resistance gene. The claimed method does not include a selection step and the specification does not teach how to obtain the desired clone in the absence of a selection step. Furthermore, the specification does not teach how to carry out methods for achieving homologous recombination. In the absence of specific guidance for achieving targeted integration of the enhancer element (i.e. incorporating the enhancer element at the desired position, upstream of the promoter, in the genome of the host cell), undue experimentation would have been required for one skilled in the art to practice the claimed method.

Claims 44 and 45 are directed to an isolated DNA construct comprising six repeats of an enhancer consisting essentially of the sequence TTCTGAGAA.

With regard to Claims 44 and 45, the specification fails to provide an enabling disclosure for the claimed DNA constructs because the specification does not teach how to use a DNA construct that does not comprise any gene. In the absence of specific guidance, one skilled in the art would not know how to use a DNA construct comprising only multiple copies of an enhancer element. Thus, the skilled artisan would have been required to engage in undue experimentation to use the claimed DNA constructs.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 5, 7-11, 19-24, 27, 34-36, 39, 40, and 46-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 19-22, 34-36, 39, 40, and 46-48 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a transfection step for getting the enhancer element into the host cell.

Claims 2, 5, 7-11, 15-17, 23, and 24 are indefinite in their recitation of "the DNA sequence of the SPI-growth hormone responsive element (SPI-GHRE)" and "the SPI-growth hormone responsive element (SPI-GHRE)" because the specification states that the nucleotide sequence of the element is SEQ ID NO:1, but the specification also often refers to "the 50 bp SPI-GHRE." However, both SEQ ID NO: 1 and the nucleotide sequence referred to as "the 50 bp SPI-GHRE" are 52 base pairs in length. Thus, the intended

meaning of the claim language is unclear. The claims do not refer to SEQ ID NO: 1. Thus, the metes and bounds of the claims are not clearly set forth.

Claims 19-22 and 34-36 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: placing the DNA construct in an environment where transcription can take place, such as a cell or a cell-free extract. The claimed method does not involve exposing the DNA construct to the apparatus for transcription. Typically, a DNA construct is transfected into a host cell where transcription can take place. DNA plus hormone is not sufficient to support transcription. In the absence of the transcriptional apparatus, no transcription can take place upon exposing a DNA construct to a hormone. Thus, transcription is not enhanced.

Claim 27 is indefinite in its recitation of a "structural" protein because the specification does not define or even discuss "structural" proteins. The specification is directed generally to any protein of interest, not just those involved in the formation of structures. Structural proteins are proteins such as collagen and keratin.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 19, 20, 41, and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoon et al., 1990.

The claims are directed to an *in vitro* method of enhancing the transcription of a gene in a DNA construct comprising a structural gene for a desired protein or polypeptide and a promoter upstream of the structural gene, wherein the method comprises providing upstream of the promoter at least one enhancer element consisting essentially of the nucleotide sequence TTC TGA GAA, and exposing the DNA construct to a hormone.

Yoon et al. reported that transcription of the serine protease inhibitor (SPI) 2.1 gene is induced by growth hormone in rat liver. Yoon et al. isolated and characterized the SPI 2.1 gene from a rat genomic library and examined the 5'-flanking region of the gene which revealed a Dnase I hypersensitive site within 500 base pairs of the transcriptional inititiation site. Portions of the 5'-flanking region were fused to a heterologous promoter and reporter gene and introduced into primary rat hepatocytes by lipofection, thereby generating expression vectors and eukaryotic host cells as instantly claimed (p. 19948, column 2). SPI 2.1 sequences from -275 to -54 gave a 2-3-fold induction of reporter gene activity in cells grown in the presence of GH, similar to the level of induction of the endogenous SPI 2.1 mRNA in isolated hepatocytes. Thus, the instantly claimed method of enhancing transcription was demonstrated for the disclosed DNA constructs by measuring induced reporter gene activity. Further definition of the essential sequences revealed that a segment from -147 to -102 could confer GH responsiveness when linked in tandem copies in front of a heterologous promoter. Reporter constructs containing six tandem copies of SPI-GHRE linked to the thymidine kinase promoter and the chloramphenicol acetyltransferase (CAT) coding sequence were significantly induced by growth hormone (p. 19951, column 1, paragraph 5). Using the gel shift assay, a nuclear factor from normal rat liver was identified which could interact with this minimal response fragment.

GH regulation of this activity was suggested by the fact that it was absent in hypophysectomized animals but reappeared 1 hour after treatment of said animals with GH.

Applicants argue that Yoon et al. does not anticipate the claimed invention because there is no teaching or suggestion in Yoon et al. of a method of providing six copies of an enhancer element comprising the nucleotide sequence TTCTGAGAA. However, as discussed above, the cited reference discloses on page 19951, column 1, paragraph 5 that six copies of SPI-GHRE were linked to a reporter construct and expression from this construct was induced by growth hormone. This element comprises the nucleotide sequence TTCTGAGAA.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 7, 15, and 23-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lindquester et al. (1989).

The claims are directed to an enhancer element comprising the nucleotide sequence TTCTGAGAA, an expression vector comprising at least one enhancer element consisting essentially of the nucleotide sequence TTCTGAGAA, an isolated eukaryotic host cell containing the expression vector, and a DNA construct comprising a promoter, a structural gene and at least one enhancer element comprising the sequence TTCTGAGAA.

Lindquester et al. (1989) disclose the nucleotide sequence of an avian tropomyosin gene. The gene includes the sequence TTCTGAGAA located in one of the introns (position 18602 of Figure 1 on page 2105). A genomic clone containing the tropomyosin gene was isolated from a quail DNA genomic library.

Since enhancer elements are known to be located in introns, the presence of the sequence TTCTGAGAA in an intron would permit it to function as an enhancer element. The hormone responsiveness of the element is an inherent property of the element. Thus, even if the hormone responsiveness of the genetic element was not recognized, the presence of the DNA sequence would confer hormone responsiveness to the disclosed gene. Furthermore, one would have been motivated to construct an expression vector comprising the tropomyosin gene and a host cell comprising said expression vector in order to produce the protein in culture. One would have anticipated a reasonable expectation of success for making the expression vector and host cell comprising the expression vector because only standard molecular biology techniques are required to make such compositions. Therefore, it would have been obvious to one of skill in the art at the time of the invention to have made an expression vector and a host cell comprising the expression vector, wherein the expression vector comprises an enhancer element including the nucleotide sequence TTCTGAGAA.

One would have been motivated to use the nucleotide sequence disclosed by Lindquester et al. to construct an expression vector and a host cell comprising the expression vector in order to produce tropomyosin in culture for further study of the protein and the regulatory sequences driving expression of the protein. The vector would have necessarily contained the enhancer element present in the gene.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Applicants argue that Lindquester et al. does not teach that the DNA sequence TTCTGAGAA may serve as an enhancer element which is responsive to both lactogenic hormones and somatogenic hormones. However, the reference need not teach that the sequence functions as an enhancer element or that it is responsive to hormones. The reference only needs to provide motivation for making an expression vector comprising the DNA sequence TTCTGAGAA such that the sequence does function as an enhancer. The reference provides adequate motivation for making an expression vector to express tropomyosin in culture. Such a vector would contain the requisite DNA sequence, which would then function as an enhancer (based on its position in the intron). The hormone responsiveness conferred by the presence of the element is an inherent property of the element. One skilled in the art need not be aware of the hormone responsiveness of the element to be motivated to make the expression vector. Thus, even if the properties of the element were not recognized by one skilled in the are, the expression vector, for which there is ample motivation to make, would still have these properties as a consequence of having the element.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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